REMARKS

The Applicants submit these remarks in response to the Final Office Action dated July 6, 2004 ("Office Action"). The five-month deadline for filing a response falls on December 6, 2004, therefore Applicants believe that this response is timely filed.

Claims 1, 5, 6, 8-17 and 22-24 are currently under consideration. The Examiner has rejected claims 1, 5, 6, 8-17 and 22-24.

The Applicants respond to these rejections as set forth below.

I. Rejections of Claims 15 and 16 under 35 U.S.C. § 112

The Examiner has maintained his rejection of claims 15 and 16 under 35 U.S.C. § 112, first paragraph for the "reasons of record." (Office Action, p. 2) In the Office Action dated February 11, 2003, the Examiner rejected claims 15 and 16 and objected to the specification under 35 U.S.C. § 112, first paragraph, as "failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited." (2/11/03 Office Action, p. 4.)

As Applicants have previously submitted, the specification discloses a fully characterized antigen, therefore Applicants can claim an antibody by its binding affinity. See Applicants' Amendment filed April 26, 2004, hereinafter "April 26, 2004 Amendment," at page 13. Applicants further believe that the specification provides adequate disclosure to teach one skilled in the art how to make the FM155 antibody without undue experimentation. However, in an effort to expedite the examination process, applicants assure the Examiner that an acceptable deposit of

hybridoma producing the antibody FM155 in compliance with 37 C.F.R. §§ 1.801 – 1.809 will be made before the date of payment of the issue fee for the instant application.

Applicants assure the Examiner that (a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request; (b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application; (c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, which ever is longer; and (d) the deposits will be replaced if they should become nonviable or non-replicable.

The Examiner has indicated that deposit of the hybridoma producing FM155 antibody would satisfy the enablement requirements. (February 11, 2003 Office Action, p. 5.) Therefore, upon deposit, withdrawal of the rejection of claims 15 and 16 under 35 U.S.C. § 112 is respectfully requested. Applicants wish to stipulate that the deposit of the hybridoma not constitute an admission of inadequate disclosure of FM155 antibody in the specification.

II. Claim Rejections—35 U.S.C. § 103(a)

The Examiner has maintained his rejections of claims 1, 5, 6, 8-17, and 22-24 under 35 U.S.C. § 103(a) over Melvin *et al.*, WO 97/00449 ("Melvin") in combination with the teachings of Newton *et al.*, Int'l. Jnl. Oncol. 6:1063-1070, 1995 ("Newton").

The Applicants respectfully traverse this rejection for the reasons set forth below.

i. The Standard for a Rejection for Obviousness Requires a Specific Showing of a Suggestion to Combine References and Consideration of Objective Evidence of Non-Obviousness

For a rejection of claims under § 103 to stand, the Examiner must present evidence sufficient to establish a prima facie case of obviousness, and the Applicant must fail to rebut that prima facie case of obviousness: "To reject claims in an application under section 103, an examiner must show an unrebutted *prima facie* case of obviousness." *In re Rouffet*, 149 F.3d 1350, 1350 (Fed. Cir. 1998).

The Federal Circuit recently reiterated the evidentiary burden required for the PTO to make a prima facie showing of obviousness based on the combination of elements found in multiple references. In *In re Lee*, 277 F.3d 1338, 61 U.S.P.Q. 2d 1430 (Fed. Cir. 2002) the Federal Circuit cited with approval cases requiring specific, particular findings as to why a skilled artisan, without knowledge of the claimed invention, would have selected elements from the references to combine into the claimed invention. *Id.* at 1343.

"'The factual inquiry whether to combine references must be thorough and searching.' *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with."

Id., at 1343, quoting *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52 (Fed. Cir. 2001)); see also, *In re Lee* at 1343 (holding that neither the examiner nor the Board adequately supported the selection and combination of the two cited references to render the claimed invention obvious), and *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985) (holding that the district court had improperly reconstructed the claimed invention from separate components of the prior art). Thus, to establish a prima facie case of obviousness, the Examiner must provide a showing of a specific suggestion, teaching, or motivation to combine prior art references.

"In the absence of a proper prima facie case of obviousness, an applicant who complies with the other statutory requirements is entitled to a patent." *In re Rouffet*, 149 F.3d, 1350 (Fed. Cir. 1998).

ii. The Examiner Has Not Established a Prima Facie Case that Melvin Combined with Newton Renders Claims 1, 5, 6, 8-17 and 22-24 Obvious

The Applicants respectfully assert that the Examiner has not satisfied the burden of providing a prima facie case of obviousness and, therefore, the rejection of claims 1, 5, 6, 8-17 and 22-24 under 35 U.S.C. § 103 is improper and should be withdrawn.

As the Examiner acknowledges in the Office Action dated February 11, 2003, "Melvin *et al.* do not teach an antagonist that inhibits angiogenesis by modifying protein-protein interactions, wherein the protein-protein interactions comprise interactions between at least one amino acid within MMP-9 **and at least one amino acid sequence within α5β1 integrin**." (2/11/03 Office Action, p. 10, emphasis in original.) The Examiner further states that "the prior art does not characterize that the protein-protein interactions 'cause MMP-9 to bind the β1-containing integrin' [...]"

Because MMP-9 and α5β1 integrin are not disclosed together either in Melvin or Newton, and because the Examiner does not demonstrate how the references would make the combination of the elements in claim 1 obvious, the Examiner has provided no motivation for one of skill in the art to combine the two references to obtain the invention of claim 1. *See In re Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (requiring a thorough and searching inquiry for a motivation to combine references). Therefore, reconsideration of the rejection of claim 1 and withdrawal of the rejection are respectfully requested.

For the reasons stated above, a *prima facie* case that claim 1 would be made obvious by Melvin in combination with Newton has not been established. Because neither Melvin nor Newton suggest, inter alia, the use of an "antagonist that inhibits angiogenesis by modifying interactions between matrix metalloproteinase 9 (MMP-9) and a ß1-containing integrin," the combination of Melvin and Newton cannot render claim 1 obvious. Therefore, neither claim 1, nor its dependent claims would be rendered obvious by Melvin in combination with Newton.

iii. The References Cited Under §103 Do Not Teach Or Suggest the Invention

As argued in the Applicants' responses of April 26, 2004 and September 8, 2003, the cited art does not teach or suggest the invention of the claims. The Examiner has found the Applicants' previous arguments unpersuasive, stating that "Melvin successfully suggests the use of therapeutic antagonists for the purpose of treating cancer wherein said antagonist interacts with at least one amino acid sequence within MMP-9 and or 'modifies protein-protein interactions, wherein the protein-protein interactions comprise interactions between at least one amino acid sequence within MMP-9.'" (Office Action, p. 4)

With all due respect, the Applicants assert that the Examiner has quoted the claim in an incomplete manner, and as a result has changed its meaning. Claim 1 previously read, in its entirety:

> An antagonist that inhibits angiogenesis by modifying protein-protein interactions, wherein the protein-protein interactions comprise interactions **between** at least one amino acid sequence within matrix metalloproteinase 9 (MMP-9) **and** at least one amino acid within a ß1-containing integrin. (emphasis added)

The word "between" by definition refers to two things, in this instance MMP-9 and ß1 integrin. By ending his quote directly after "MMP-9," the Examiner

has left out the second half of the phrase, thus ignoring ß1 integrin, the second item to which the claim term "between" refers. As a result, the Examiner has concluded that "the claims do not require that MMP9 bind directly to integrins." (Office Action, p. 5)

As described above, the language of claim 1 requires interactions between MMP-9 and ß1-containing integrin. Claim 16 as amended requires binding to a polypeptide consisting of the sequence of SEQ ID NO: 1 and new claim 26 requires that the antagonist of claim 16 be monoclonal antibody FM155. Support for new claim 26 is found in the Specification, *e.g.* in original claim 15. The peptide of SEQ ID NO:1 was identified as described in Example 7 (Specification, p. 34) This peptide was found to bind to MMP-9 and to inhibit MMP-9-α5ß1 integrin interactions. Nowhere is the peptide of SEQ ID NO: 1 described in either Melvin or Newton

Thus, neither Melvin or Newton teach or suggest the antagonists of claim 1 or claim 16. Nonetheless, a clarifying amendment to claim 1 has been made, to recite an antibody that "inhibits angiogenesis by modifying interactions between matrix metalloproteinase 9 (MMP-9) and a ß1-containing integrin." This amendment does not alter the meaning of the claim or introduce new subject matter, but simply makes clear that claim 1 requires that **MMP-9 binds directly to a ß1-containing integrin** and that the **antagonist** of the present invention **modifies this binding**.

The Examiner also finds the Applicants' arguments, that the present invention is a non-obvious subgenus of the larger genus disclosed by Melvin, to be nonpersuasive. According to the Examiner, "[a]pplicants have not demonstrated that the claims define a particular species because, as set forth previously, the claims encompasses [sic] a genus of antagonists. Also, the claims do not require that MMP9 bind directly to integrins." (Office Action, p. 5) As a first matter, the Examiner appears to be arguing that in order to distinguish from the genus of

Melvin the Applicants are required to demonstrate that their invention is a particular species before being found non-obvious over Melvin.

The Applicants respectfully assert that an invention can be a non-obvious subgenus of a larger genus previously described in the art. In *In re Lemin*, 322 F2d 839, 141 U.S.P.Q. 814, (C.C.P.A. 1964), the Court reversed the Board's affirmation, of rejections of claims to a subgenus of herbicides as obvious over broader genus claims. As previously quoted in part by the Applicants in the April 26, 2004 Amendment, the Court wrote that:

> The position of the Patent Office is, essentially, that Lemin has done no more than pluck a subgenus out of a generic disclosure by Jones, and has used that subgenus in precisely the manner taught by Jones.
>
> Generally speaking there is nothing unobvious in choosing "some" among "many" indiscriminately. In re Rosicky, 47 CCPA 859, 276 F.2d 656, 125 USPQ 341. Here, however, the choice is based on a discovery by Lemin that some compounds, falling within a prior art genus, have a special significance.

Id., at 841. The C.C.P.A. wrote that "[i]t is clear that Jones [the cited art] broadly discloses the instant compounds, as defined in claims 1 and 11." *Id.*, at 840. The structural range of compounds disclosed by Lemin *et al.*, however, was found to be "a critical factor in the herbicidal activity of the instant compounds. Since there is nothing in the cited art to suggest the criticality of that range, we do not find that limitation obvious." *Id.*, at 841.

As stated in the April 26, 2004 Amendment at pages 15-19, it was not known or expected in the art that proteolytic enzymes such as MMPs may bind directly to integrins and that a modification of an interaction between a proteolytic enzyme and an integrin may inhibit angiogenesis and/or tumor growth. As further explained in detail, neither Melvin or Newton teach or suggest antagonists that modify interactions between MMP-9 and β1-containing integrins. (*Id.*) Thus,

members of the subgenus of claim 1, *i.e.*, antagonists that inhibit angiogenesis by modifying interactions between MMP-9 and a β1-containing integrin, have a "special significance" as described in *In re Lemin* and should be found non-obvious over a combination of Melvin and Newton.

Neither Melvin or Newton teach or suggest antagonists having binding specificity for a polypeptide consisting of the sequence of SEQ ID NO: 1, as required by claim 16. Therefore, members of the subgenus of claim 16 also have a "special significance" and should be found non-obvious over a combination of Melvin and Newton.

In view of the clarifying amendments made to claims 1 and 16, as well as the arguments set forth above, the Applicants believe that the Examiner's rejection of these claims under 35 U.S.C. § 103 to have been overcome. Claims 5, 6, 8-15, 17, 22, 23 and 24 depend from claim 1 and therefore are not obvious over the cited art for at least the same reasons as claim 1. Thus, the Applicants believe that the claims rejected under 35 U.S.C. § 103 are in condition for allowance and respectfully request that the Examiner withdraw his rejection.

III. Rejections of Claims 1, 5, 6, 8-14, 16, 17 and 22-24 under 35 U.S.C. § 112

The Examiner has maintained his rejection of claims 1, 5, 6, 8-14, 16-17 and 22-24 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. (Office Action, p. 5) In the Office Action mailed December 23, 2003 ("December 23, 2003 Office Action"), the Examiner wrote that:

> The instant disclosure of a single species of a peptide and an antibody that binds to said peptide fails to adequately describe the scope of the claimed genus (any antagonist), which encompasses a substantial variety of subgenera-, i.e. peptides, organic molecules, enzymes, antibodies or oligonucleotides (page 9, line 1).

(December 23, 2003 Office Action, p. 6)

The Examiner cited *University of Rochester v. G. D. Searle & Co.*, 358 F.3d 916, 69 USPQ2d 1886 (Fed. Cir. Feb. 13, 2004) as clarifying that the standard set by *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), *i.e.*, that "[a] description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to the genus that 'constitute a substantial portion of the genus'" also applies to compounds other than cDNAs. (Office Action, p. 6.)

As an initial matter, the Applicants respectfully assert that the specification discloses more than "a single species of a peptide and an antibody that binds to said peptide," and that therefore the genus is described in the specification by a recitation of a "representative number of species falling within the scope of the genus." Figure 9, which is described in Example 9 (Specification, p. 35, ll. 15-25), shows the binding specificity of five monoclonal antibodies generated by immunization of mice with FRIP-1 peptide. At least three of these five antibodies, designated FM132, FM158, and FM155, showed greater specificity for FRIP-1 than for the control peptide AAA. One of skill in the art would reasonably expect that because the antibodies FM132 and FM158 also specifically bind FRIP-1, that they would inhibit angiogenesis as FM155 was shown to do. Therefore, at least four species of the genus, the FRIP-1 peptide and three antibodies, are disclosed.

Additionally, the Applicants respectfully draw the Examiner's attention to the fact that in *University of Rochester v. G. D. Searle & Co.*, 358 F.3d 916, 69 USPQ2d 1886 (Fed. Cir. Feb. 13, 2004), the patent at issue disclosed no representative species.

According to the Court:

> The patent's claims all require a COX-2-selective compound, but no COX-2-selective compound is disclosed

> in the patent, and it is undisputed that there was no pre-existing awareness in the art of any compound having COX-2-selective activity.

Id., at 1897, emphasis added. Further, the Court concluded:

> In sum, because the '850 patent does not provide any guidance that would steer the skilled practitioner toward compounds that can be used to carry out the claimed methods—an essential element of every claim of that patent—and has not provided evidence that any such compounds were otherwise within the knowledge of a person of ordinary skill in the art 9 at the relevant time, Rochester has failed to raise any question of material fact whether the named inventors disclosed the claimed invention.

Id, emphasis added. Therefore, the Applicants respectfully assert that this case bears limited similarity to the present situation, in which copious guidance regarding identification of the claimed antagonists, as well as at least four representative claimed species, are disclosed.

The Applicants believe that the above arguments overcome the rejection of claims 1, 5, 6, 8-14, 16-17 and 22-24 under 35 U.S.C. § 112, first paragraph, and respectfully request that the Examiner allow the claims. However, to expedite prosecution, independent claim 1 has been amended to limit the antagonist to an antibody or a peptide and independent claim 16 has been amended to limit the antagonist to an antibody. Since, as discussed above, antibodies and peptides falling within the claimed genus are disclosed in the Specification, the Applicant respectfully requests that the rejection under § 112 be withdrawn.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
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